THE JOURNAL OF INVESTIGATIVE DERMATOLOGY Vol. 47, No. 6
 Printed in U.S.A

EFFECT OF CYCLIC ADMINISTRATION OF CONJUGATED EQUINE ESTROGENS ON SEBUM PRODUCTION IN WOMEN*

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In the treatment of acne with estrogens, a method commonly used in women is the administration of the estrogen for cyclic periods of 10–14 days up to the onset of menses. With such a treatment schedule there are interval periods of 2 or more weeks wherein no drug is administered. Since the secretion of the sebaceous glands, which are primarily responsible for the inflammatory lesions in acne (1), can be suppressed by the exogenous administration of adequate amounts of estrogen (2, 3), it seemed reasonable to question whether such intermittent therapy could effect significant sebaceous gland suppression. Therefore, the present report will detail the results of sebum production studies comparing 2-week and 3-week cycles of oral administration of conjugated equine estrogens to women.

MATERIALS AND METHODS

Twenty-two female subjects, age 16 to 29, comprised the study group;† eight had acne of varying severity. Conjugated equine estrogens (Premarin®)‡ were administered orally in 30 separate drug trials, ranging in duration from 19 to 24 weeks. Six subjects received 2 or 3 separate trials involving different dose schedules. The estrogen was administered either in 2-week cycles or in 3-week cycles. With the *2-week* cycles, medication was begun at mid-cycle and continued for 14 days to the onset of menses. This procedure was repeated in subsequent cycles for the duration of the treatment period. With this treatment schedule, doses of conjugated equine estrogens, ranging from 2.5 mg to 7.5 mg daily, were administered in 12 individual drug trials to 10 subjects. With *3-week* cyclic administration, the estrogen was started on the 5th day of menses and continued for 21 days. On drug withdrawal, menses usually ensued in 2 or 3 days, and medication was reinstituted either on day 5 of menses or no later than the 7th interval day. In the 3-week treatment group, an oral progestin, medroxyprogesterone acetate (Provera®), was concomitantly administered in a dose of 10 mg a day in the last 5 days of each drug cycle in order to allow for regular cyclic bleeding on withdrawal of medication. With this treatment schedule, doses of conjugated equine estrogens, from 1.25 mg to 7.5 mg daily, were administered in 18 separate drug trials to 15 subjects.

In each subject, sebum production measurements were carried out with the use of a quantitative gravimetric procedure reported by us previously (4). An average of 6 weekly sebum measurements were made prior to drug administration. The subjects were then tested weekly during the entire period of estrogen treatment although in a few cases testing was done less often.

RESULTS

Table I lists the data for sebum production in the group of 10 subjects administered various dosages of conjugated equine estrogens in 2-week cycles. Since sebaceous gland suppression from estrogen, when it occurs, is often not evident until the 3rd month or more, the mean sebum value from estrogen treatment for all the subjects in the study was that calculated as the average of all values obtained after the 8th week of drug administration. A significant decrease in sebaceous gland activity was observed in only 2 instances, namely subject 1 receiving 7.5 mg daily and subject 6 with 5.0 mg daily. Subjects 3, 4, 9 and 10 had acne. There was no improvement in their disease, as might have been expected since sebaceous gland suppression did not occur.

In Table II are shown the sebum production values in the subjects administered conjugated equine estrogens in 3-week cycles, in doses ranging from 1.25 to 7.5 mg per day. A signifi-

This investigation was supported in part by research grants AM 07084 and AM 07388, and graduate training grant 2A-5295, National Institute of Arthritis and Metabolic Diseases, United States Public Health Service.

Presented at the Twenty-seventh Annual Meeting of The Society for Investigative Dermatology, Inc., Chicago, Ill., June 27, 1966.

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TABLE I

Sebum production (mg/10 cm²/3 hr) during 2-week cyclic administration of conjugated equine estrogens

Dose	Subject	Mean pretreatment sebum	Mean sebum, 4-week periods						Mean treatment* sebum	Per cent Suppression	P value
			1–4	5–8	9–12	13–16	17–20	21–24			
7.5 mg daily	1	3.60	2.79	2.50	2.67	2.48	2.62	—	2.60	28%	<.001
	2	4.07	4.23	3.99	4.13	4.23	4.34	3.07	4.05	None	—
	3†	3.24	3.80	3.37	3.39	4.30	2.71	3.48	3.41	None	—
	4†	2.24	2.79	3.02	2.81	2.09	2.21	2.11	2.38	None	—
	5	3.78	4.36	4.27	4.13	4.75	3.56	—	4.13	None	—
5.0 mg daily	6	3.66	3.72	2.28	2.32	2.40	2.21	—	2.26	37%	<.001
	7	2.34	2.17	2.32	2.17	2.17	1.99	1.74	2.05	12%	NS
	5	3.82	3.89	4.48	3.69	3.99	3.29	2.96	3.52	8%	NS
	4†	2.56	2.60	3.02	2.81	2.88	2.58	2.36	2.60	None	—
2.5 mg daily	8	2.03	2.09	1.53	2.03	1.96	1.78	—	1.82	10%	NS
	9†	3.62	3.72	5.08	3.00	3.84	3.62	—	3.43	5%	NS
	10†	3.04	2.71	3.56	2.90	3.00	3.14	—	3.02	None	—

* Average of all sebum values after 8th week of drug administration.
† Acne.

TABLE II

Sebum production (mg/10 cm²/3 hr) during 3-week cyclic administration of conjugated equine estrogens

Dose	Subject	Mean pretreatment sebum	Mean sebum, 4-week periods						Mean treatment* sebum	Per cent Suppression	P value
			1–4	5–8	9–12	13–16	17–20	21–24			
7.5 mg daily	4†	3.12	3.64	2.48	2.36	2.45	2.07	—	2.28	27%	<.01
	11	5.29	4.84	4.15	3.95	—	3.84	—	3.91	26%	<.01
	12	3.35	3.17	3.04	2.62	2.45	2.52	—	2.52	25%	<.01
	5	4.73	4.01	4.19	4.19	4.56	3.16	—	3.99	16%	NS
5.0 mg daily	6	3.66	3.31	2.96	2.90	2.42	2.47	1.88	2.47	33%	<.001
	7	2.98	1.84	1.92	2.17	2.14	2.28	1.42	2.11	29%	<.02
	13	3.04	2.94	2.83	2.50	2.17	2.01	1.92	2.19	28%	<.01
	14†	1.20	1.09	1.34	0.99	0.81	0.95	—	0.93	23%	<.01
	15†	2.45	2.79	2.50	2.58	2.03	1.90	1.94	2.15	12%	NS
2.5 mg daily	16	4.34	3.69	3.45	3.20	3.84	3.04	—	3.35	23%	<.05
	15†	2.03	2.30	1.66	1.90	1.47	1.88	1.66	1.78	12%	NS
	13	2.77	2.50	3.16	2.75	2.36	2.58	2.17	2.52	9%	NS
	17†	5.21	5.72	6.00	5.37	4.86	4.88	4.34	4.95	5%	NS
	18†	3.18	3.35	3.04	3.39	3.41	2.92	2.71	3.14	1%	NS
	19	2.50	1.86	1.82	2.67	2.19	2.90	2.09	2.50	None	—
1.25 mg daily	20	2.36	1.96	2.26	2.19	2.26	1.88	—	2.09	11%	NS
	21	1.70	2.47	1.84	1.78	1.70	1.61	—	1.72	None	—
	22	1.30	1.55	1.45	1.57	1.86	1.26	—	1.45	None	—

* Average of all sebum values after 8th week of drug administration.
† Acne.

TABLE III

Comparisons of sebaceous gland responses in individuals receiving different dose schedules of conjugated equine estrogens

Subject	Dose schedule	Per cent sebum suppression	P value
4	7.5 mg; 3-week cycles	27%	<.01
	7.5 mg; 2-week cycles	None	—
	5.0 mg; 2-week cycles	None	—
7	5.0 mg; 3-week cycles	29%	<.02
	5.0 mg; 2-week cycles	12%	NS
13	5.0 mg; 3-week cycles	28%	<.01
	2.5 mg; 3-week cycles	9%	NS
6	5.0 mg; 3-week cycles	33%	<.001
	5.0 mg; 2-week cycles	37%	<.001
5	7.5 mg; 3-week cycles	16%	NS
	7.5 mg; 2-week cycles	None	—
	5.0 mg; 2-week cycles	8%	NS
15	5.0 mg; 3-week cycles	12%	NS
	2.5 mg; 3-week cycles	12%	NS

cant reduction in sebum secretion was seen in 3 out of 4 subjects receiving 7.5 mg daily, and in 4 out of 5 individuals administered 5.0 mg daily. Only one subject (※16) out of 6 demonstrated a sebum-suppressive effect from 2.5 mg daily, and none of the 3 subjects on 1.25 mg daily showed a response. Five cases had acne (subjects 4, 14, 15, 17, 18). In only 2 cases (subjects 4 and 14) did the acne improve, and in both instances they showed a significant fall in sebum output.

Six subjects received more than one course of drug administration. Table III compares the sebaceous gland responses for the various dose schedules given to each of these subjects. It can be seen that both the dose of drug (*e.g.* subject 13) and the schedule of its administration (*e.g.* subjects 4 and 7) are important factors in determining sebaceous gland responsiveness. It should also be noted that relatively high doses, whether administered in 2-week or 3-week cycles, may fail to suppress glandular activity (*e.g.* subjects 5 and 15).

DISCUSSION

The present studies have demonstrated that a minimum daily dose of 5.0 mg of conjugated equine estrogens is, in essence, required for significant suppression of sebaceous gland activity in women. The schedule of drug administration is also important since with drug amounts of 5.0 mg and 7.5 mg, a significant decrease in sebum production was observed in 7 out of 9 subjects receiving 3-week cyclic treatment but in only 2 out of 9 receiving 2-week cyclic treatment.

The observations from this investigation of the relative ineffectiveness of 2-week cyclic administration of oral conjugated equine estrogens on sebaceous gland secretion lend corroboration to the clinical studies reported by Torre and Klumpp (5). They found that the post-ovulatory cyclic administration of conjugated equine estrogens to females with acne required in the vast majority of instances 5.0 mg or more daily for satisfactory control of the disease. As mentioned previously, there were 8 patients in the present study with acne. In only two did the condition improve, and these were the only patients of the group with a fall in sebum production from estrogen. There was no apparent relationship between the response of the sebaceous glands and the presence or absence of acne before treatment.

Mention should be made of the effect on the menstrual periods from the estrogen administered to the subjects in this study. Of those receiving 3-week cyclic treatment (combined, as described above, with an oral progestin in the last 5 days of each drug cycle), only one, a subject taking 5.0 mg a day, experienced menstrual difficulty consisting of 2 separate episodes of breakthrough bleeding. By contrast, in the group receiving 2-week cyclic drug administration, 5 out of 12 subjects noted changes in the menstrual cycles. The menses *per se* were not particularly abnormal, but the intervals between periods became decidedly irregular.

SUMMARY

Conjugated equine estrogens, in oral doses of 1.25 to 7.5 mg daily, were administered cyclically for 2-week or 3-week periods for 19–24 weeks to 22 female subjects in 30 separate drug trials. The purpose was to study the effect of this estrogen in various dose schedules on sebaceous gland secretion. The results were as follows: 1) in 12 trials of 2-week cyclic treatment, sebum production was decreased significantly in only 2

instances (dosages of 5.0 and 7.5 mg); 2) in 18 trials of 3-week cyclic treatment, a significant reduction of sebum secretion occurred in most subjects receiving 5.0 and 7.5 mg daily; and 3) of eight subjects with acne, only two were improved, these being the only patients among those with acne showing significant sebaceous gland inhibition.

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